

## Growth Hormone

### Introduction:

- Growth Hormone (GH) is also called somatotropic hormone or somatotropin.
- It is the primary hormone responsible for regulating overall body growth (somato means "body").
- It is secreted by somatotropes of anterior pituitary gland.

### Mechanism of Action:

- It is a protein hormone consisting of a single peptide chain of 191 amino acids.
- It is easily transported in blood plasma.
- However, it is not able to pass through the lipid bilayers of target cells. Instead it binds to a specific receptor located on the outer surface of cell membrane.
- It acts through "Tyrosine Kinase Receptor".

### Physiological Effects:

#### I- Effect on Growth:

- It causes growth of almost all tissues of the body that are capable of growing.
- It stimulates growth of both skeleton & soft tissues.
- It promotes increase in size (Hypertrophy) & number (Hyperplasia) of cells.
- GH increases the size of cells through favoring protein synthesis (by stimulating almost all aspects of protein synthesis, while simultaneously inhibiting protein degradation).
- GH increases the number of cells by stimulating cell division and by preventing apoptosis (programmed cell death).

##### a) Effect on Skeleton (Bone & Cartilage):

- Increases bone growth both in length (linear) & in thickness.
- This effect is indirect mediated through *somatomedins*.
- Somatomedins acts on bone & cartilage to promote their growth by:
  - Proliferation of epiphyseal cartilage.
  - Deposition of chondroitin sulfate at epiphyseal plate.
  - Increases uptake of sulfur.
  - Increases  $\text{Ca}^{+2}$  &  $\text{PO}_4^{-3}$  in bones.
  - Increases collagen synthesis.
  - Increases osteoblastic activity.

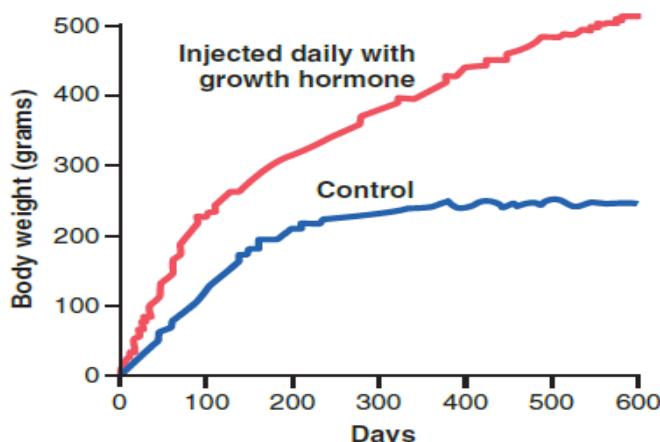
##### Somatomedins:

- They are proteins synthesized in the liver.
- Somatomedin (or sulphation factor) is the original name.

- Now, these peptide mediators are preferentially called **Insulin-like Growth Factors (IGFs)** because they are structurally and functionally similar to insulin.
- IGFs exert their effects by binding with specific receptor on the target cell "Tyrosine Kinase Receptor".
- There are 2 types; IGF-I & IGF-II.
- The most important one is somatomedin C which is also called IGF-I
- GH acts through somatomedin C = IGF-I
- IGF-I synthesis is stimulated by GH and mediates most of this hormone's growth-promoting actions.

b) Effect on Soft Tissues:

- Generally, GH increases organ size & function.
- Increases muscle mass (= lean body mass).
- This effect is mediated through:
  - Increases amino acid uptake.
  - Increases protein synthesis.
  - Increased DNA, RNA synthesis.
  - Increased cell size and number.



Comparison of weight gain of a rat injected daily with GH with that of normal control.

II- Effect on Metabolism:

- This effect is direct.
- GH binds directly to its target organs, namely:
  - Liver.
  - Adipose tissue.
  - Skeletal muscles.

a) Effect on Protein metabolism:

- GH increases total body protein.

- It has an *anabolic* effect.
- The role of GH on protein metabolism include:
  - Increases amino acid uptake (= enhancement of amino acid transport through the cell membrane).
  - Stimulation of protein synthesis.
  - Increases RNA synthesis.
  - Inhibits protein catabolism (= protein sparing effect).
  - Produces +ve nitrogen balance.

b) Effect on Carbohydrate metabolism:

- GH increases blood glucose level (= Hyperglycemia) & prevents its utilization for energy production.
- It has a *diabetogenic* effect.
- The role of GH on carbohydrate metabolism include:
  - Increases hepatic glucose output (stimulate glycogenolysis & gluconeogenesis).
  - Decreases glucose uptake & utilization by adipose tissue & muscles (= anti-insulin effect).
  - Causes compensatory increase in insulin secretion → insulin resistance.

c) Effect on Lipid metabolism:

- GH enhances Fatty Acids (FA) utilization for energy production.
- It has a *lipolytic* effect.
- The role of GH on lipid metabolism include:
  - Increases mobilization of FA from adipose tissue (= stimulation of lipolysis), through activation of hormone sensitive lipase → fatty liver.
  - Stimulation FA oxidation → production of ketone bodies (Ketogenesis).

d) Effect on Electrolytes:

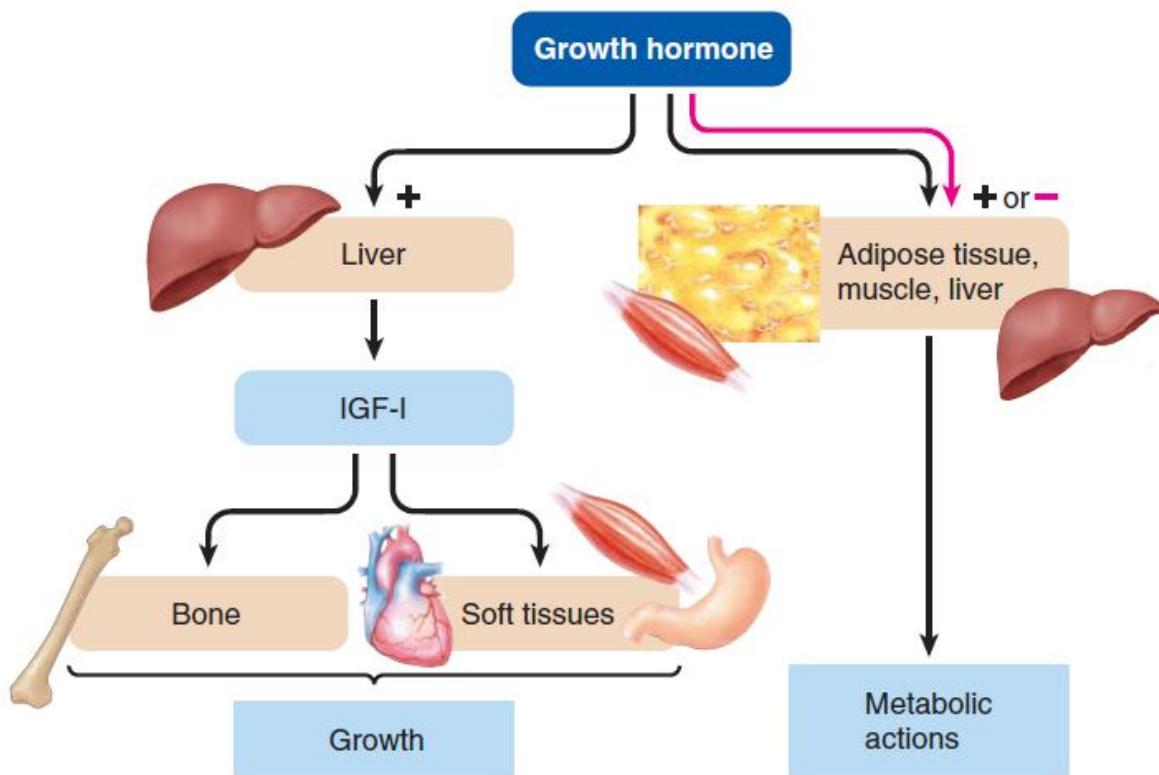
The role of GH on electrolytes includes:

- Increases the intestinal absorption of  $\text{Ca}^{++}$  (by stimulating vitamin D production).
- Elevates plasma  $\text{PO}_4^{3-}$  level.
- Reduces  $\text{Na}^+$  and  $\text{K}^+$  excretion by an action independent of the adrenal glands, probably because these electrolytes are diverted from the kidneys to the growing tissues.

☺ N.B:

GH is Anabolic, Lipolytic, Ketogenic & Diabetogenic

- GH ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass.



Functions of GH secretion

### Regulation of Secretion:

The release of GH is under control of:

- I- Hypothalamic hormones.
- II- Feedback loop.
- III- Diurnal rhythm.
- IV- Other factors.

#### I- Hypothalamic Hormones:

- Two antagonistic regulatory hormones from the hypothalamus are involved in controlling GH secretion:
  - a) **Growth Hormone Releasing Hormone (GHRH)**, which is stimulatory & dominant.
  - b) **Growth Hormone Inhibiting Hormone (GHIH, or somatostatin)**, which is inhibitory.
- The hypothalamic GHRH & GHIH are secreted by nerve endings in the median eminence of the hypothalamus.
- Then they will be transported from there to the anterior pituitary gland in the hypothalamic – hypophyseal portal blood.
- Both GHRH and somatostatin act on the anterior pituitary somatotropes by binding with G-protein coupled receptors linked to the cAMP second-messenger pathway.

- GHRH increasing the cAMP, while somatostatin decreasing cAMP.

## II- Feedback Loop:

- 1) GH stimulates IGF-I secretion by the liver, and IGF-I in turn is the *primary inhibitor* of GH secretion by the anterior pituitary as follows:
  - a) IGF-I directly inhibits the somatotropes in the anterior pituitary.
  - b) IGF-I inhibits GHRH-secreting cells and stimulates the somatostatin-secreting cells in the hypothalamus.
- 2) GH itself inhibits hypothalamic GHRH secretion & stimulates somatostatin release.

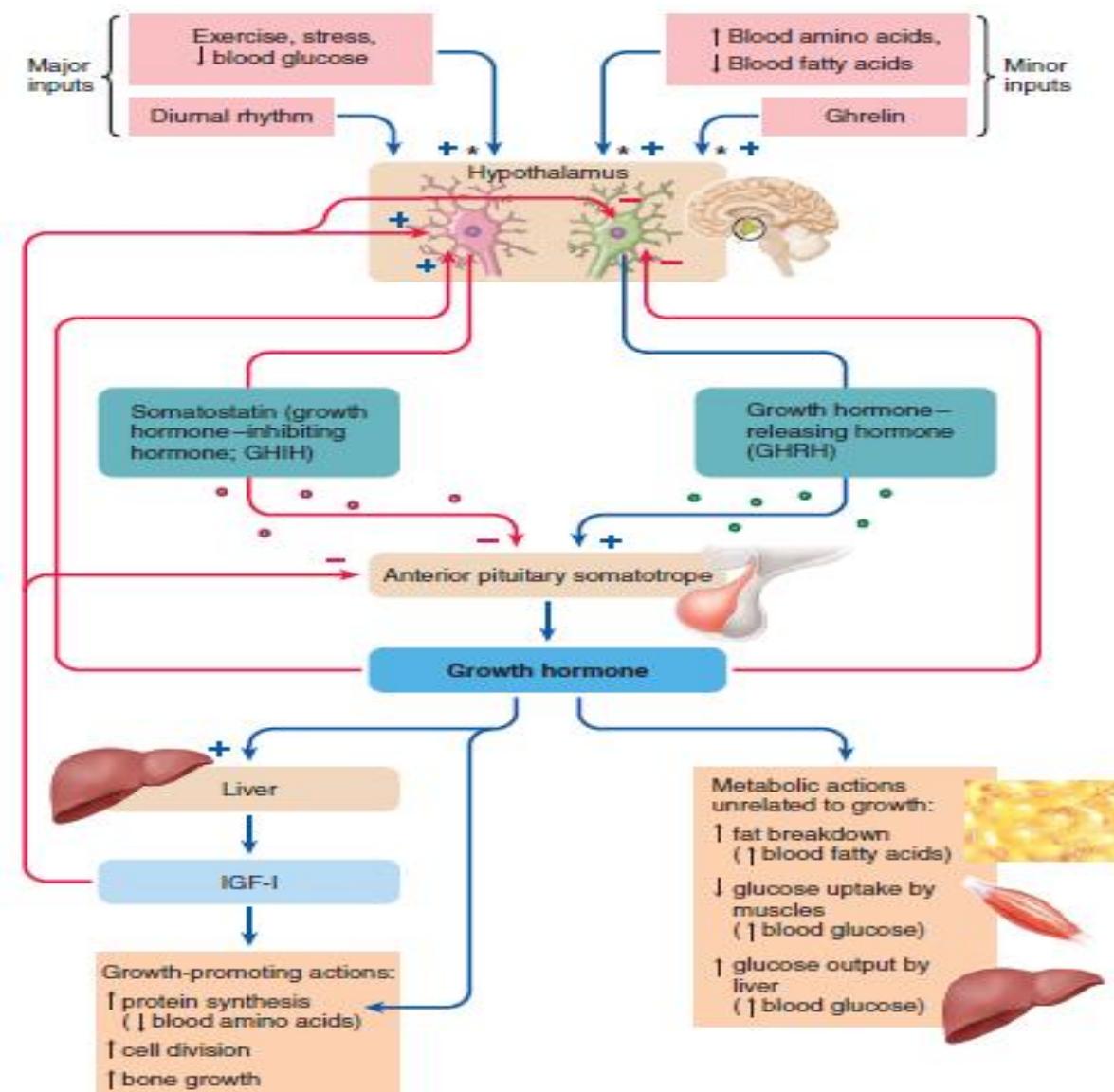
## III- Diurnal Rhythm:

- GH is secreted in a pulsatile pattern, increasing & decreasing.
- Most of the day, growth hormone levels tend to be low and constant.
- After the onset (about an hour) of deep sleep, GH secretion increases up to five times the daytime value.
- It rapidly drops over the next several hours.

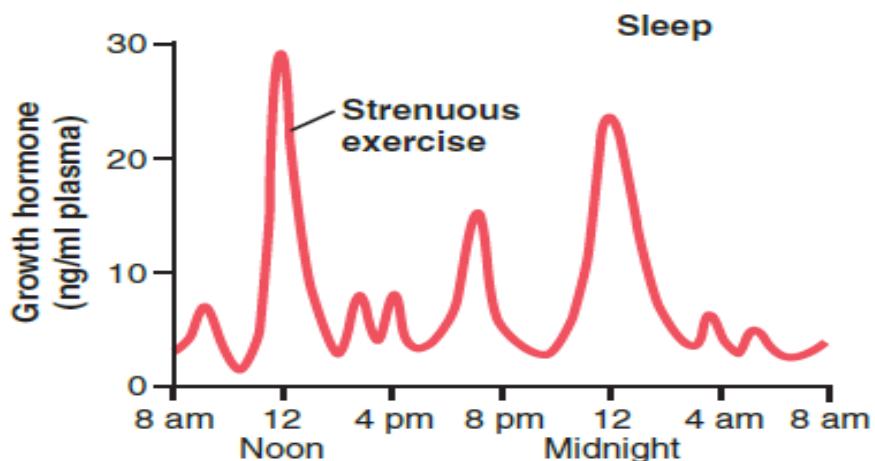
## IV- Other Factors:

Superimposed on this diurnal fluctuation in GH secretion are further bursts in secretion that occur in response to:

- a) Deficiency of energy substrates:
  - Lowered blood glucose level (= Hypoglycemia), the most potent factor.
  - Decreased blood FA level.
  - Fasting.
  - Starvation.
- b) Stressful stimuli:
  - Exercise.
  - Excitement.
  - Trauma.
- c) Rise in blood amino acids level:
  - After high protein meal (GH promotes the use of these amino acids for protein synthesis).
- d) Other hormones:
  - Thyroid hormones.
  - Sex hormones (androgens & estrogens).



### Control of GH secretion



Variations in GH secretion throughout the day

☞ Blood levels of GH & age:

- For many years it was believed that GH was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue.
- After adolescence, GH secretion decreases slowly with aging.
- The smaller amount of GH secreted in adult is needed to maintain the metabolic functions.

	ng/ml
5 to 20 years	6
20 to 40 years	3
40 to 70 years	1.6

### Disturbances of GH Secretion:

#### 1) Hyper-secretion of GH:

- Cause:
  - Tumor of the GH-producing cells of the anterior pituitary (mainly).
  - Hypothalamic tumor secreting GHRH (rare).
- Manifestations:
  - Depending on the age of the individual when the abnormal secretion begins.
  - Clinically presented as: Gigantism or Acromegaly.

	<b>Gigantism</b>	<b>Acromegaly</b>
<b>Pathology</b>	<ul style="list-style-type: none"> <li>- Increased secretion of GH before puberty</li> <li>- Before closure of epiphyseal plates</li> </ul>	<ul style="list-style-type: none"> <li>- Increased secretion of GH after puberty</li> <li>- After closure of epiphyseal plates</li> </ul>
<b>Cause</b>	Tumor of the GH-producing cells of the anterior pituitary	
	<p style="text-align: center;"><b>I- Effect on Growth</b></p> <p style="text-align: center;">a) <u>Skeleton (Bones &amp; Cartilage) :</u></p>	
	<ul style="list-style-type: none"> <li>• Symmetrical enlargement of the body (= no distortion of body proportions)</li> <li>• Overgrowth of long bones</li> </ul>	<ul style="list-style-type: none"> <li>• Asymmetrical enlargement of the body</li> <li>• Overgrowth of acral (terminal) parts of the skeleton</li> <li>• Acro = extremity, Megaly = large</li> </ul>

## Clinical Picture

<ul style="list-style-type: none"> <li>Height increases above 2 meters</li> </ul>	<ul style="list-style-type: none"> <li>No increase in height</li> <li>Bones become thicker</li> <li>Overgrowth of small bones of hands, feet &amp; cancellous membranous bones</li> <li>Fingers are broad &amp; sausage-like (= Spade-like hand)</li> <li>Large skull (= Box-shaped)</li> <li>Proinent supra-orbital ridges</li> <li>Large protruded mandible (= Prognathism), with wide spaced teeth</li> <li>Enlargement of vertebrae → deformities &amp; kyphosis</li> <li>Osteoarthritis &amp; joint pains</li> <li>Increased cartilagenous growth → enlargement of nose &amp; ears</li> </ul>
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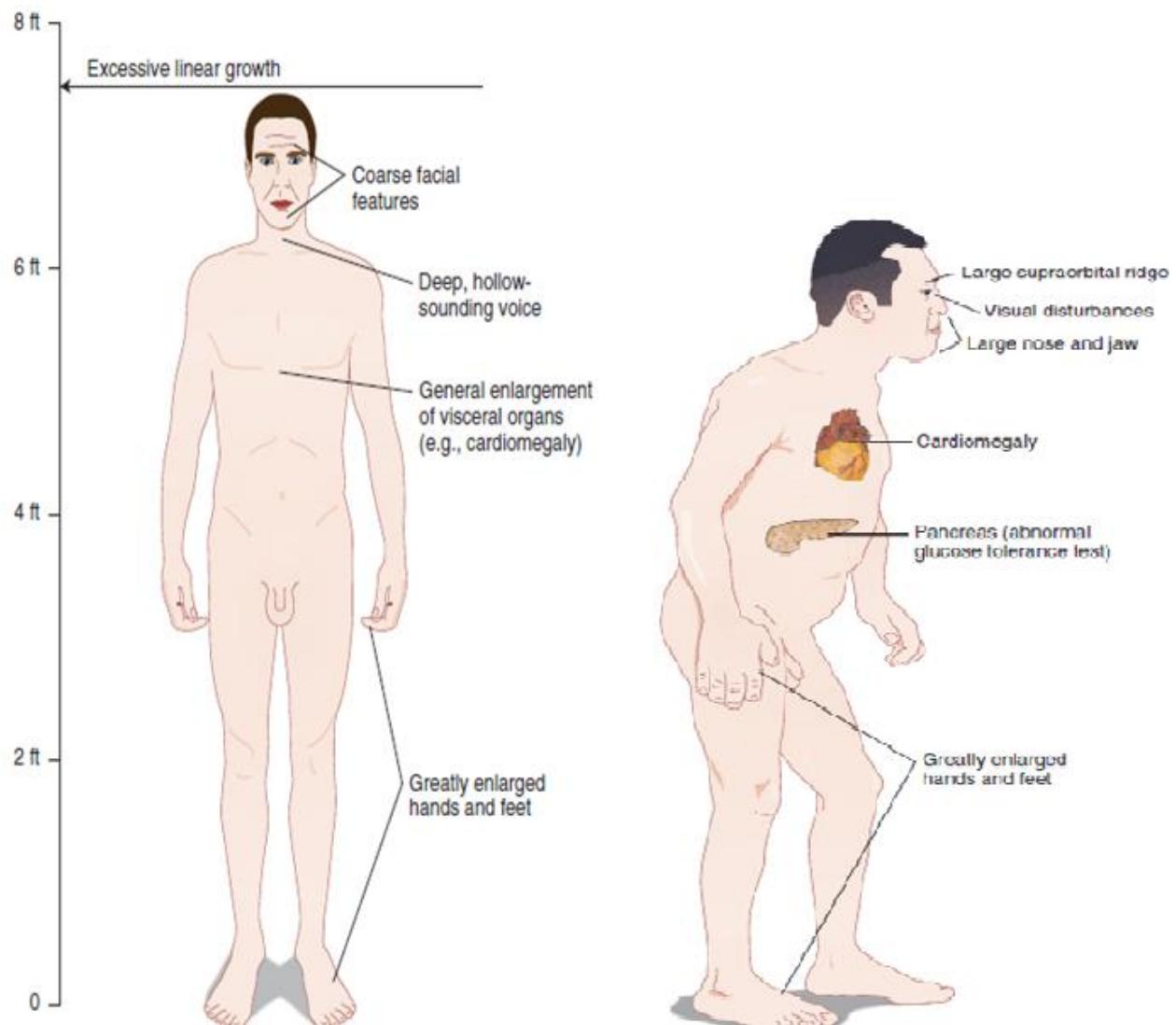
### b) Soft Tissues:

<ul style="list-style-type: none"> <li>Enlargement of internal organs (hepatomegaly, splenomegaly, cardiomegaly)</li> <li>Increased muscular strength (initially)</li> </ul>	<ul style="list-style-type: none"> <li>Overgrowth of connective tissues &amp; skin (glands &amp; hairs)</li> <li>Facial features are coarse (= Ape-like)</li> <li>Thick lips &amp; large tongue</li> <li>Thickened, wrinkled skin (due to overgrowth of connective tissue) with excessive sweating &amp; sebaceous secretion</li> <li>Overgrowth of soft tissues of scalp (= Bull dog scalp)</li> <li>Overgrowth of body hair</li> <li>Hypertrophy of larynx → Deep &amp; husky voice</li> </ul>
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## II- Endocrinological Disturbances

<ul style="list-style-type: none"> <li>Increased blood glucose level (Hyperglycemia, Diabetes Mellitus) due to anti-insulin effect</li> <li>Gonadal atrophy (= Hypogonadism) leading to: (♀♂) <ul style="list-style-type: none"> <li>In ♀ → Amenorrhea (stoppage of menstruation)</li> <li>In ♂ → Impotence (no erection)</li> </ul> </li> <li>Gynecomastia (= enlarged breast) &amp; Galactorrhea (= increased milk secretion) (♀♂)</li> </ul>
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<b>III-Other Manifestations</b>	
	<ul style="list-style-type: none"> <li>• Hypertension (⌚?)</li> <li>• Peripheral nerve disorders (⌚?)</li> <li>• Visual disturbances (⌚?)</li> </ul>
<b>Diagnosis</b>	<ol style="list-style-type: none"> <li>1. <u>Clinical Picture:</u> See before</li> <li>2. <u>Investigations:</u> <ol style="list-style-type: none"> <li>a) Hormonal assay ( GH level)</li> <li>b) Radiological examinations ( CAT scan &amp; MRI)</li> </ol> </li> </ol>
<b>Treatment</b>	<ol style="list-style-type: none"> <li>1. Surgical Removal</li> <li>2. Hormonal replacement therapy</li> </ol>

**Gigantism****Acromegaly**

## 2) Hypo-secretion of GH:

- In most cases, GH deficiency occurs before puberty.
- Clinically presented as: Pituitary Dwarfism or Pituitary Infantilism

### ➤ Pituitary Dwarfism

#### Pathology:

- It is due to deficiency of GH before puberty.

#### Cause:

1. Hypothalamic disorder:
  - Absence of GHRH.
2. Pituitary disorder:
  - Absence of GH (inherent deficiency).
  - Secretion of inactive GH.
  - Organic lesion or surgical removal of pituitary.
3. Lack of somatotropins:
  - The liver is unable to secrete somatotropins IGF-I.
4. End organ resistance:
  - Due to receptor defect (= Laron dwarfism).

#### Clinical Picture:

- a) Effect on growth:
  - Symmetrical growth retardation both in *skeleton & soft tissues*.
  - Stunted growth all over the body, so the proportions are that of a child.
  - Height: 100 – 120 cm (Short stature = Dwarf).
- b) Normal mentality.
- c) Normal sexual development.

### ➤ Pituitary Infantilism

#### Pathology:

- It is due to deficiency of GH & gonadotropins (both before puberty).

#### Clinical Picture:

#### Dwarfism & Hypogonadism

- a) Effect on growth:
  - As pituitary dwarfism (see before).
- b) Normal mentality.
- c) Sexual retardation (= Hypogonadism):
  - Secondary sex organs remain infantile.
  - The sexual characters do not appear.



The effect of abnormalities in GH secretion on growth

### ☺ Deficiency of GH after puberty:

- GH deficiency in adulthood after growth is already complete produces relatively few symptoms, including:
  - Reduced skeletal muscle mass & strength (because of less muscle protein).
  - Poor exercise performance.
  - Decreased bone density (less osteoblast activity).
  - Hypoglycemia.
  - Progeria (= rapid & premature aging).

## Physiology of Growth

### Introduction:

- Growth is a complex phenomenon characteristic of living organism.
- It is accompanied by orderly sequence of maturational changes.
- Growth requires:

- Net synthesis of proteins
- Lengthening of the long bones (the bones of the extremities).
- Increases in the size and number of cells in the soft tissues.
- Weight gain alone is not synonymous with growth because weight gain may occur from retaining excess water or storing fat without true structural growth of tissues.
- Although, growth hormone is absolutely essential for growth, it is not wholly responsible for determining the rate and final magnitude of growth in a given individual.

## Factors Influencing Growth:

- 1) Genetic Factors
- 2) Adequate Diet:
  - This is the most important extrinsic factor affecting growth.
  - The diet must contains:
    - Sufficient amount of proteins with essential amino acids.
    - Essential vitamins & minerals.
    - Adequate calories, so that ingested proteins is not burned for energy production.
- 3) Freedom from chronic diseases and stressful conditions.
- 4) Hormonal Factors:
  - Normal hormonal levels are essential for growth.
  - The hormones required for growth include:
    - Growth hormone (the most important).
    - Thyroid hormones.
    - Insulin hormone.
    - Sex hormones.
    - Glucocorticoids.

## Hormonal Control of Growth:

1. Growth Hormone:
  - Peak action:
    - GH is highest during *adolescence*, the period of most rapid growth.
    - The importance of GH in human growth is from time of birth till 16 years old.
  - Net effect:
    - Stimulate replication (mitosis) of most cells.
    - Promote bone growth & lengthening (indirect through IGF-I).
    - Stimulate protein synthesis in most tissues (direct) → Hypertrophy.
2. Thyroid Hormones:
  - Peak action:

- Thyroid Hormones (TH) are important for CNS development during *intrauterine life* & *first few months after birth*.
- The importance of TH in human growth is in the first 4 years of life, then decreasing effect till the age of 20.
- Net effect:
  - Potentiating the actions of IGF-I.
  - Stimulate the secretion of GH.
  - Needed for normal function (= Permissive effect).
  - Promote bone growth & lengthening (particularly long bones).
  - Stimulate protein synthesis (anabolic effect).

### 3. Insulin Hormone:

- Peak action:
  - Insulin exerts some growth promoting effect *during childhood*.
  - An insulin hormone is highly important during intrauterine life.
- Net effect:
  - Promote cell differentiation & mitosis during intrauterine life.
  - Stimulate the secretion of IGF-I.
  - It can bind & activate IGF-receptors.
  - Stimulate protein synthesis (anabolic effect).

### 4. Sex Hormones:

- Peak action:
  - They are responsible for pubertal growth spurt.
- Net effect:
  - Powerful stimulant for protein synthesis (anabolic effect) in many organs.
  - Stimulate the secretion of GH & IGF-I.
  - Stimulate linear bone growth, at the same time, *promote closure of epiphyseal plates* (this dual effect explains the pattern seen in adolescence; rapid lengthening of bones followed by complete cessation of growth for life).



### Anabolic Steroids:

- They are testosterone like agents, used by athletes to increase their muscle mass & strength.

### 5. Glucocorticoids:

- These are hormones secreted from adrenal cortex.
- The most known hormone is cortisol.
- They inhibit growth, if administrated in a high dose during growth periods of life.
- Mechanism:

- Inhibit the secretion of GH.
- Inhibit protein synthesis.
- Stimulate protein degradation (catabolic effect).

## Growth Periods:

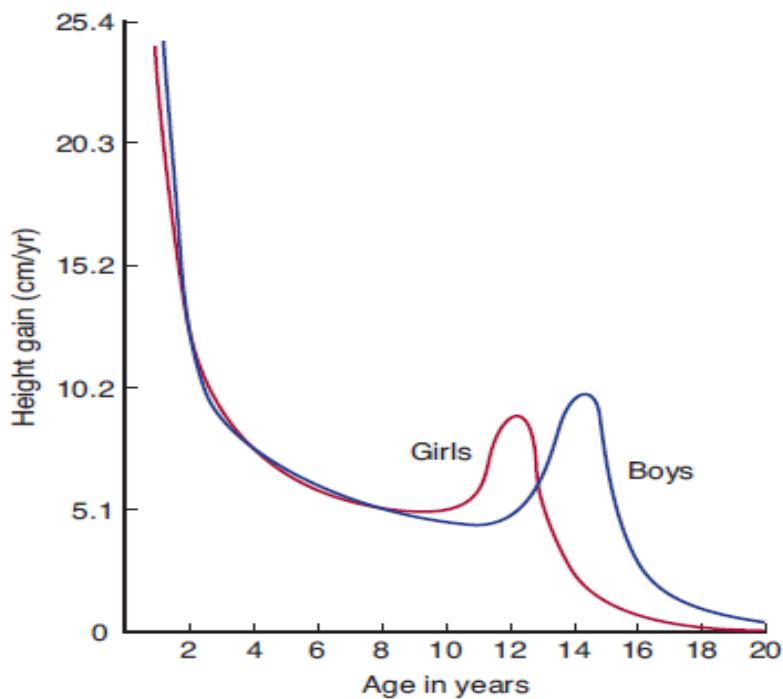
- The rate of growth is not continuous.
- Also, the factors responsible for promoting growth are not the same throughout the growth period.
- Growth periods are divided into:

### I- Intra-uterine:

- Hormonal control:
  - Placental hormones (mainly).
  - Insulin & IGF-II (major role).
  - Thyroid hormones (especially for CNS development).
  - GH has **no role** at all during this period.

### II- After Birth:

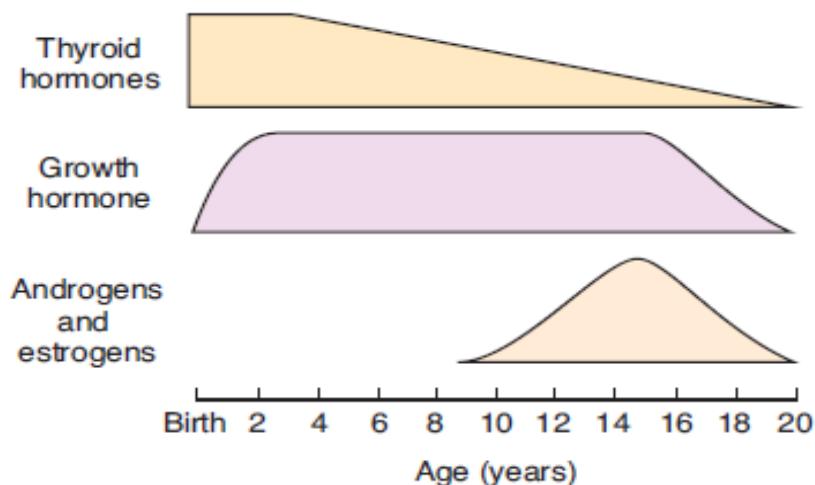
- Children display two periods of rapid growth:
  - a) Post-natal (= neonatal) growth spurt:
    - During the first 2 years of life.
    - The growth is markedly accelerated.
    - Hormonal control (Thyroid hormones & GH).
  - b) Pubertal growth spurt:
    - During adolescence.
    - At puberty, a marked acceleration in linear growth takes place because the long bones lengthen.
    - Puberty begins at about age 11 in girls and 13 in boys and lasts for several years in both sexes.
    - Hormonal control (sex hormones & GH).



Rate of growth in boys and girls from birth to age 20

Intra-uterine life	After Birth		
	Post-natal (Growth Spurt)	In between	Pubertal (Growth Spurt)
• Placental Hormones	• Thyroid hormones	• Growth hormone	• Sex hormones
• Insulin Hormone	• Growth hormone		• Growth hormone
• IGF-II			
• Thyroid hormones			

Hormonal control of growth



Relative importance of hormones in human growth at various ages

## Short Individuals

### Introduction:

- The terms "dwarf" (= little person) is used to describe a person of short stature.
- Dwarfism, also known as short stature, occurs when an organism is extremely small.
- In humans, it is defined as an adult height of less than 4 feet 10 inches (58 in; 147 cm), regardless of sex, although some individuals with dwarfism are slightly taller.

### Types of Dwarfism:

#### I- Proportionate:

- It is a form of simple short stature, without any deformities.
- Both limbs & trunk are small.

#### II- Disproportionate:

- Characterized by either short limbs or a short trunk.

### Causes of Short Stature:

#### 1) Familial:

- Runs in families due to hereditary causes.

#### 2) Genetic:

- Due to gene defect or mutation.

#### 3) Nutritional:

- Including:
  - Malnutrition (especially low protein intake).
  - Malabsorption.
  - Metabolic disorders.

4) Environmental stress:

- Chronic abuse and neglect can also cause dwarfism in children, independent of malnutrition.

5) Chronic diseases:

- Including:
  - Cardiac.
  - Pulmonary.
  - Renal.
  - Immunological diseases.
  - Cancer.

6) Skeletal problems:

- Including:
  - Bone diseases.
  - Cartilage diseases.

7) Endocrinological diseases:

- A) Hypothalamic:
  - Decreased production of GHRH.
- B) Pituitary:
  - Pituitary Dwarfism:
    - It is due to defect in GH only.
    - Causes: see before.
  - Pituitary Infantilism:
    - It is due to defect in GH & gonadotropins.
  - Pan-hypopituitarism:
    - It is due to defect in all anterior pituitary hormones.
- C) Thyroid:
  - Decreased production of thyroid hormones early in life.
  - Hypothyroidism in infants termed "cretinism".
- D) Adrenal:
  - Excessive production of glucocorticoids hormones "Cushing's Syndrome".
  - Cortisol therapy.
- E) Pancreatic:
  - Deficient insulin hormone as in type-1 diabetes mellitus.
- F) Gonadal:
  - Precocious Puberty:
    - Causing early closure of bone epiphyses.

8) Unknown cause:

- In many cases there is no known cause.
- It is termed "constitutional delayed growth".